Complete Summary

GUIDELINE TITLE

2002 national guideline for the management of lymphogranuloma venereum.

BIBLIOGRAPHIC SOURCE(S)

Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD). 2002 national guideline for the management of lymphogranuloma venereum. London: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD); 2002. Various p. [28 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Lymphogranuloma venereum (also known as Durand-Nicolas-Favre's disease, lymphopatia venereum, and lymphogranuloma inguinale)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Infectious Diseases
Obstetrics and Gynecology
Urology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To present a national guideline on the management of lymphogranuloma venereum

TARGET POPULATION

Patients in the United Kingdom with lymphogranuloma venereum

INTERVENTIONS AND PRACTICES CONSIDERED

Assessment/Diagnosis

1. Assessment of clinical features
2. Collection of genital specimens containing cellular material
3. Laboratory diagnostic techniques:
    - Culture on cycloheximide treated McCoy cells of material from suspected lymphogranuloma venereum lesion
    - Direct immunofluorescence (DIF) of material from suspected lymphogranuloma venereum lesion to demonstrate Chlamydia trachomatis elementary and inclusion bodies
    - Enzyme immunoassay (EIA) for ulcer scrapes or bubo aspirates, but not for rectal samples (should be confirmed by a blocking test or another method)
    - Deoxyribonucleic acid (DNA) amplification techniques such as the ligase chain reaction (LCR) or polymerase chain reaction (PCR) to detect nucleic acid
    - Positive Chlamydia trachomatis serology. Three types of techniques: complement fixation test, the single L-type immunofluorescence test, and the micro-immunofluorescence test

Treatment/Management

1. Pharmacological interventions:
    - Doxycycline
    - Erythromycin
    - Co-trimoxazole
    - Tetracycline
    - Minocycline

    Note: Azithromycin in multiple doses over 2-3 weeks was considered, but not recommended.

2. Fluctuant buboes aspirated through healthy adjacent skin.
3. Clinical follow-up until signs and symptoms have resolved.

4. Surgical repair, including reconstructive genital surgery, in patients with fibrotic lesions or fistulas that are beyond the stage where chemotherapy can be used.
5. Partner examination, testing for urethral or cervical chlamydial infection, and treatment as needed.

MAJOR OUTCOMES CONSIDERED

- Labour intensiveness, expense, sensitivity, specificity, and availability of diagnostic techniques
- Efficacy and cost of pharmacological treatment

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The previous guidelines from 1998 were largely based on the published U.S. Centers for Disease Control and Prevention (CDC) Guidelines for Treatment of Sexually Transmitted Diseases of 1993 and 1997, and on a Medline search spanning the years 1966-1998. The guideline has been updated by searching Medline from 1998-2000 using the search terms: "Lymphogranuloma venereum"; "Chlamydia trachomatis diagnosis"; and "Chlamydia trachomatis treatment". There were no entries in the Cochrane Library of any randomized clinical trials on Lymphogranuloma venereum. In addition abstracts and proceedings from the International Conferences on AIDS, Meetings of the International Society for STD Research (ISSTDR), and Symposia on Human Chlamydial Infections over the last decade were reviewed.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence:

Ia

- Evidence obtained from meta-analysis of randomised controlled trials

Ib

- Evidence obtained from at least one randomised controlled trial

IIa

- Evidence obtained from at least one well designed controlled study without randomisation

IIb

- Evidence obtained from at least one other type of well designed quasi-experimental study

III

- Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies, and case control studies

IV

- Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The revision process commenced with authors being invited to modify and update their 1999 guidelines. These revised versions were posted on the website for a 3 month period and comments invited. The Clinical Effectiveness Group and the authors concerned considered all suggestions and agreed on any modifications to be made.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grading of Recommendations:

A (Evidence Levels Ia, Ib)

- Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.

B (Evidence Levels IIa, IIb, III)

- Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.

C (Evidence Level IV)

- Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities.
- Indicates absence of directly applicable studies of good quality.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The initial versions of the guidelines were sent to the following for review:

- Clinical Effectiveness Group (CEG) members
- Chairs of UK Regional GU Medicine Audit Committees who had responded to an invitation to comment on them
- Chair of the Genitourinary Nurses Association (GUNA)
- President of the Society of Health Advisers in Sexually Transmitted Diseases (SHASTD)
- Clinical Effectiveness Committee of the Faculty of Family Planning and Reproductive Health Care (FFP)

Comments were relayed to the authors and attempts made to reach a consensus on points of contention with ultimate editorial control resting with the Clinical Effectiveness Group. Finally, all the guidelines were ratified by the councils of the two parent societies.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Levels of evidence (I-IV) and grades of recommendation (A-C) are defined at the end of the "Major Recommendations" field.

Diagnosis

The diagnosis of lymphogranuloma venereum (LVG) is often differential, after other causes of genital ulceration or inguinal lymphadenopathy has been ruled out. Even when lymphogranuloma venereum is suspected, investigations for other potentially co-existing sexually transmitted infections must be undertaken, in particular for syphilis.

Positive diagnosis of lymphogranuloma venereum is difficult, requiring a combination of good clinical acumen and supportive investigations. Lymphogranuloma venereum can be suspected on positive chlamydia serology, isolation of Chlamydia trachomatis either from the infected site or histological identification of Chlamydia in infected tissue.

Collection of genital specimens

Chlamydiae are intracellular organisms so samples must contain cellular material that can be obtained:

- By aspiration from fluctuant lymph nodes/buboes; after topical disinfection, a 20 gauge needle should be inserted into the lymph node through healthy adjacent tissue and the pus aspirated into a syringe; saline solution may be injected and re-aspirated
- From the ulcer base exudate or from rectal tissue
- Bubo pus is best homogenised in tissue culture medium before inoculation (Van Dyck & Piot, 1992)

Main diagnostic techniques

(i) Culture on cycloheximide treated McCoy cells of material from lymphogranuloma venereum lesion is the most specific method, but its sensitivity is 75-85% at best, and often closer to 30-50% in the case of bubo aspirate (Perine & Stamm, 1999); this is in part due to the toxic effect of the pus on the culture cells; the method is labour intensive, expensive, and of restricted availability.

or

(ii) Direct immunofluorescence (DIF) of material from suspected lymphogranuloma venereum lesion to demonstrate Chlamydia trachomatis elementary and inclusion bodies; this method can be sensitive but requires expertise (subjective interpretation) and is labour intensive.

or

(iii) Enzyme immunoassay (EIA) is a convenient and objective method, suitable for ulcer scrapes or bubo aspirates, but not for rectal samples; sensitivity is lower than other methods (75-80% compared with culture) and should be confirmed by a blocking test or another method; unsuitable for test of cure.

or

(iv) Detection of nucleic acid (DNA) by amplification techniques such as the ligase chain reaction (LCR) or polymerase chain reaction (PCR); these methods are becoming established for routine testing of urethral, cervical, or urine specimens but have rarely been used in the context of lymphogranuloma venereum (Hadfield, 1995; Kellock, 1997); they are highly sensitive and specific, but expensive and requiring dedicated laboratories; they are unsuitable for test of cure.

or

(v) Positive Chlamydia trachomatis serology. Three types of techniques have been used: complement fixation (CF) test, the single L-type immunofluorescence test, and the micro-immunofluorescence test, the latter one being the most accurate serological assay. In general, a fourfold rise of antibody (both immunoglobulin M [IgM] and immunoglobulin G [IgG]) in the course of suspected illness is diagnostic of active infection. The major disadvantage is that this test is only performed in a few specialized laboratories.

Other methods

- The original diagnostic method for lymphogranuloma venereum from the 1930s until 1970s was the Frei test which consisted of intradermal injections of purified Chlamydia trachomatis antigen obtained from culture in yolk sacs of chicken embryos. The test was reportedly positive in about 95% of bubonic lymphogranuloma venereum or late complications. Given its lack of sensitivity and specificity, the commercial manufacture of the test has been abandoned in 1974. (Perine & Stamm, 1999)
- Histology of the lymph nodes show follicular hyperplasia and abscesses is non-specific.

Methods (i) through (iv) are unable to distinguish lymphogranuloma strains from other chlamydial serotypes, usually. Recently, investigators in Sheffield were able to combine several molecular diagnostic techniques, using polymerase chain reaction detecting the major outer membrane protein (MOMP) gene of Chlamydia trachomatis and restriction fragment length polymorphism (RFLP) analysis to perform serovar typing from the patient's lymph node aspirate. (Kellock et al., 1997) In most case series, only methods (i) and (ii) have been used for the recovery of Chlamydia trachomatis or the micro-immunofluorescence among serological methods. Micro- immunofluorescence is the only serological means of distinguishing between different serotypes of Chlamydia trachomatis and is therefore the diagnostic test of choice, although developments in polymerase chain reaction technology make this test the most promising diagnostic tool.

Management

General advice

1. Patients should be advised to avoid unprotected sexual intercourse until they and their partner(s) have completed treatment and follow-up.
2. Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of

themselves and their partner(s). This should be reinforced by giving them clear and accurate written information.

Further investigations

Screening for other possible causes of genital ulcerative disease should be arranged, i.e. diagnosis of Haemophilus ducreyi, Treponema pallidum, Herpes simplex and Klebsiella/Calymmatobacterium granulomatis (see related guidelines titled 2002 National Guideline for the Management of Chancroid; 2002 National Guidelines for the Management of Early Syphilis; 2002 National Guidelines for the Management of Late Syphilis; 2002 National Guideline for the Management of Genital Herpes; and 2002 National Guideline for the Management of Donovanosis [Granuloma Inguinale]). In addition screening for serological syphilis and possibly for HIV should be offered.

Lymph node biopsy may be used to make differential diagnoses with atypical infections and neoplasia.

Treatment

No controlled double blind treatment trials have been published on lymphogranuloma venereum. The low incidence of the disease, its complex presentation and its natural history, marked by spontaneous remissions and exacerbations, have precluded any rigorous evaluation of management. Only one single comparative trial published in 1957, had demonstrated that the duration of buboes in patients receiving tetracycline, sulfadiazine, or chloramphenicol was significantly shorter than in symptomatically treated patients. (Greaves et al., 1957) Subsequent observations have reported the successful use of tetracycline, minocycline, and rifampicin. Early treatment is important to reduce the chronic phase. Prolonged treatment (at least 3 weeks) is the norm and more than one course of therapy (see Table 1, below), alternating antibiotics may be necessary for chronic cases. (Piot & Holmes, 1990; Toomey & Barnes, 1990)

On the basis of the known response of Chlamydia trachomatis to antibiotics such as doxycycline, tetracycline, erythromycin in uncomplicated infections, the following recommendations have been made (see Table 1, below):

Recommended regimens:

- 1st choice: doxycycline 100 mg two times daily orally for 21 days (or other cyclines such as tetracycline 2g daily or minocycline 300 mg loading dose followed by 200 mg twice daily) (Level of Evidence III or IV, Grade of Recommendation B) (Greaves et al., 1957; Osoba, 1983; Piot & Holmes, 1990; Toomey & Barnes, 1990; Perine & Stamm, 1999)
- 2nd choice: erythromycin 500 mg four times daily orally for 21 days (Level of Evidence IV, Grade of Recommendation B) (Bowie, 1982; Osoba, 1983; Piot & Holmes, 1990)

Alternative regimens

- The activity of azithromycin against Chlamydia trachomatis suggests that it may be effective in multiple doses over 2-3 weeks but clinical data on its use are lacking.
- These treatments are identical to those of U.S. Centers for Disease Control and Prevention (CDC) guidelines published in 1997 (CDC, 1997). The recent Sheffield case was treated with a 3-week course of minocycline.

Allergy

Patients allergic to cyclines should be treated with the erythromycin regimen.

Treatment for pregnant or lactating mothers

Pregnant and lactating women should be treated with the erythromycin regimen.

Accompanying measures

Fluctuant buboes should be aspirated through healthy adjacent skin and surgical incision is usually contraindicated by fear of complications.

Sexual Partner(s) Management

Persons who have had sexual contacts with a patient who has lymphogranuloma venereum within the 30 days before onset of the patient's symptoms should be examined, tested for urethral or cervical chlamydial infection, and treated, or receive presumptive treatment.

Follow-up

Patients should be followed clinically until signs and symptoms have resolved. This may occur within 3 to 6 weeks. However, there is also evidence of spontaneous remission within 8 weeks. Routine microbiological test of cure is not easily done depending on diagnostic methods.

Patients with fibrotic lesions or fistulas are beyond the stage where chemotherapy can be used and surgical repair, including reconstructive genital surgery, often must be considered.

Special Considerations

Latent lymphogranuloma venereum may be reactivated in patients with human immunodeficiency virus (HIV) infection with development of multiple abscesses. (Van Dyck & Piot, 1992) HIV infected patients should be treated following the regimens previously cited. Prolonged therapy may be required and delay in resolution may occur.

Table 1. Drugs Shown to be Effective in the Treatment of Lymphogranuloma Venereum (modified by the National Guideline Clearinghouse [NGC])

Drug	Dose	Route	Grading of Recommendation	Level of Evidence
Co-trimoxazole	80/400 mg twice daily	Oral	C	IV
Doxycycline*	100 mg twice daily	Oral	B/C	IV
Erythromycin*	500 mg four times daily	Oral	C	IV
Minocycline	300 mg loading dose, followed by 200 mg twice daily	Oral	C	IV
Tetracycline	500 mg four times daily	Oral	C/B	III

Note: There have been numerous randomised trials to prove the equivalent efficacies of doxycycline, erythromycin, tetracycline, minocycline, etc, for the management of uncomplicated Chlamydia trachomatis infections, however these are lacking for lymphogranuloma venereum; a B grade is conferred for simplicity of use for doxycycline.

*Recommended by U.S. Centers for Disease Control and Prevention (CDC, 1997).

Definitions:

Levels of Evidence:

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- Evidence obtained from meta-analysis of randomised controlled trials

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C (Evidence Level IV)

- Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities.
- Indicates absence of directly applicable studies of good quality.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

No controlled double blind treatment trials have been published on lymphogranuloma venereum. The type of supporting evidence is graded and identified for select recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate diagnosis and management of patients with lymphogranuloma venereum; early treatment is important to reduce the chronic phase of the condition

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- No controlled double blind treatment trials have been published on lymphogranuloma venereum. The low incidence of the disease, its complex presentation and its natural history, marked by spontaneous remissions and exacerbations, have precluded any rigorous evaluation of management.
- Human immunodeficiency virus (HIV) infected patients may require prolonged therapy. Delay in resolution may occur.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The Clinical Effectiveness Group reminds the reader that guidelines in themselves are of no use unless they are implemented systematically. The following auditable outcome measure is provided:

- All cases of suspected lymphogranuloma venereum should be subjected to laboratory investigations. Target 100%. Sexual partners should be treated. Serological syphilis and HIV testing should be offered.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD). 2002 national guideline for the management of lymphogranuloma venereum. London: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD); 2002. Various p. [28 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 Aug (revised 2002)

GUIDELINE DEVELOPER(S)

Association for Genitourinary Medicine - Medical Specialty Society
Medical Society for the Study of Venereal Diseases - Disease Specific Society

SOURCE(S) OF FUNDING

Not stated

GUIDELINE COMMITTEE

Clinical Effectiveness Group (CEG)

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Author: Philippe Mayaud and Duncan McCormick

Clinical Effectiveness Group (CEG) Members: Keith Radcliffe (Chairman); Imtyaz Ahmed-Jushuf; Jan Welch; Mark FitzGerald; Janet Wilson

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Conflict of interest: None

GUIDELINE STATUS

This is the current release of the guideline. This guideline updates a previously released version.

An update is not in progress at this time.

GUIDELINE AVAILABILITY

Electronic copies: Available in HTML format from the Association for Genitourinary Medicine (AGUM) Web site. Also available in Portable Document Format (PDF) from the Medical Society for the Study of Venereal Diseases (MSSVD) Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following background documents are available:

- UK national guidelines on sexually transmitted infections and closely related conditions. Introduction. Sex Transm Infect 1999 Aug;75(Suppl 1):S2-3. Electronic copies: Available in Portable Document Format (PDF) from the Medical Society for the Study of Venereal Diseases (MSSVD) Web site.
- Revised UK national guidelines on sexually transmitted infections and closely related conditions 2002. Sex Transm Infect 2002;78:81-2.

Print copies: For further information, please contact the journal publisher, BMJ Publishing Group.

The following related guidelines are available:

- 2002 national guideline for the management of chancroid. London: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD); 2002. Various p. See the National Guideline Clearinghouse (NGC) summary.
- 2002 national guidelines for the management of early syphilis. London: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD); 2002. Various p. See the National Guideline Clearinghouse (NGC) summary.
- 2002 national guidelines for the management of late syphilis. London: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD); 2002. Various p. See the National Guideline Clearinghouse (NGC) summary.
- 2002 national guideline for the management of genital herpes. London: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD); 2002. Various p. See the National Guideline Clearinghouse (NGC) summary.
- 2002 national guideline for the management of donovanosis [granuloma inguinale]. London: Association for Genitourinary Medicine (AGUM), Medical

Society for the Study of Venereal Disease (MSSVD); 2002. Various p. See the National Guideline Clearinghouse (NGC) summary.

Electronic copies: Available in HTML format from the Association for Genitourinary Medicine (AGUM) Web site. Also available in Portable Document Format (PDF) from the Medical Society for the Study of Venereal Diseases (MSSVD) Web site.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on December 8, 2000. The information was verified by the guideline developer on January 12, 2001. This summary was updated on June 24, 2002.

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Date Modified: 4/12/2004